National Institute of Allergy and Infectious Diseases
Division of Acquired Immunodeficiency Syndrome

Network Leadership Meeting

December 9, 20003
Fernwood Building, Conference Rooms 2C21-2C23
10401 Fernwood Road, Bethesda, Maryland

DAIDS convened a meeting of the leadership of its trials networks on December 9, 2003 at the Fernwood Building, 10401 Fernwood Road, Bethesda, Maryland to discuss ongoing issues of reorganization and recompetition of those networks.

Network leaders participating included:

Dr. Constance Benson (AACTG) (chair),
Dr. Ward Cates (HPTN),
Dr. Gerald Friedland (CPCRA),
Dr. Julie McElrath (HVTN),
Dr. James Neaton (CPCRA),
Dr. Paul Palumbo (PACTG),
Dr. William Powderly (AACTG),
Dr. Robert Schooley (AACTG),
Dr. Stephen Spector (PACTG),
Dr. Judith Wasserheit (HVTN).

DAIDS representatives included:

Dr. Edmund Tramont, Director, DAIDS
Dr. Jonathan Kagan, Deputy Director, DAIDS
Dr. Carl Dieffenbach, Director, Basic Sciences Program
Dr. Jonathan Fishbein, Director, Office of Policy in Clinical Research & Operations
Dr. Margaret (Peggy) Johnston, Director, Vaccine and Prevention Research Program
Dr. Sandra Lehrman, Director, Therapeutics Research Program
Mr. Matthew Murguia, Director, Office of Program Operations and Scientific Operations
Mr. Daniel C. Montoya, Senior Policy Advisor, Henry M. Jackson Foundation
Maureen Power, Nurse Consultant, Office of Policy in Clinical Research & Operations
Dr. Deborah Birx Walter Reed Army Institute of Research (WRAIR)

Director's Guidance

Dr. Tramont offered a context within which the discussions should occur. He said that recent articles in the Los Angeles Times and Wall Street Journal have raised anew questions of financial conflicts of interest and oversight of NIH-sponsored research, which in turn have prompted questions from Congress.

The dynamics of the epidemic have changed because of the impact of HAART and the shift in focus to the international arena. Estimates are that individual physicians are caring for 50-70% of HIV-infected persons in the U.S. Furthermore, the African American community has expressed interest in participating to a greater extent in clinical trials, as evident from a meeting the previous day with members of that community.

Dr. Tramont said it was unlikely that Congress will appropriate substantial additional funding for AIDS. The $15 billion for the President's Emergency Fund for AIDS Relief has set the bar and there is a sense that "they have given at the office." Given the anticipated large demand on resources for vaccine and microbicides trials, dollars are tight and prioritization and reprogramming must occur, but he is "confident that we will be able to get what we need."

During discussion the question was raised as to how responsibility for research will be structured between NIH and the Department of State. Dr. Tramont said that situation remains confusing; the law says that research should be under the purview of the Ambassador, yet that office should not conduct research.

Dr. Tramont noted that many members of the public and politicians have a view of research as being conducted by lone scientists, when in fact clinical research is conducted by teams of researchers. He pointed out that the four nations in the developing world that have best contained the epidemic – Uganda, Senegal, Brazil, Thailand – are the ones that have been the most research-driven in their responses.

Research helps to build infrastructure; training is the first step in expanding access to care. He recounted the debacle of introducing infant formula into developing countries. Inadequate training and explanation of how to use the product led to it being stretched out and watered down, resulting in malnutrition in the infants who received watery formula.

His greatest concern is that this is the first time that a public health issue has been the basis for a major foreign policy initiative. Failure likely will stifle further initiatives in this area.

It was suggested that the administration's mantra should become ABC-R, adding research to the prevention framework developed in Uganda.

DAIDS also noted that NCI is interested in reintegrating its agenda into the networks. At this point the network recompetition is solely DAIDS, but at some point it may embrace program activities from other Institutes, particularly with regard to laboratory capacity for research on OIs.

Overview

Dr. Benson, who chaired the meeting, said the purpose of the meeting is to develop a plan that will detail areas of scientific coordination, integration, resource sharing, and increased efficiencies in the areas identified by the network leadership during previous discussions. DAIDS will consider this input in developing their fiscal year 2006 initiatives.

The "very enthusiastic timeline" envisions a report from this group by close of business on December 19. It was suggested that the group focus on defining the targets rather than on the formal date of the report. The timeline is driven by the need to send materials to the AIDS Research Advisory Committee (ARAC) in advance of their January meeting, to provide a framework of what they will hear in greater detail at the May ARAC meeting.

Guiding Network Principles

- The networks are the framework and scientific and intellectual "engines" that drive the research agenda.

- The networks will be held accountable for:
    - Developing the research agenda
    - Developing and maintaining investigator and site expertise to implement the research agenda
    - Developing and initiating protocols to address the research agenda
    - Fostering coordination and integration where scientifically appropriate across research areas

Guiding Principles – Leadership

- Network leadership will be responsible for:
    - Directing and coordinating network activities to achieve research agenda objectives
    - Developing metrics/monitoring performance of sites and laboratories specific to network functions
    - Allocation of funds based on protocol and site performance
    - Accountability to DAIDS/NIAID leadership
- DAIDS-Network Leadership Working Group will:
    - Assist with cross-network prioritization, coordination, and integration
    - Allocation of funds for large, complex, or high-resource utilization protocols

The idea has been floated that a portion of the allocation for each trial network be retained in a "bank" for use on common projects that go beyond the scope of what individual networks are capable of implementing.

The role of the Partnership for AIDS Vaccine Evaluation (PAVE) working group was questioned. DAIDS considers PAVE to be a body which coordinates implementation rather than as an advisory body—which must follow a different set of regulations with regard to public openness. Vaccine priorities will have to be integrated into the total research program.

It was noted that the size of phase II/III trials can be very different depending on whether the context is therapy or prevention, with the later generally requiring larger numbers of participants and often a longer period of follow-up. The leadership group wanted to "flag this to come back to" in order to get a better shared sense of understanding of where the threshold lays in moving from a trial conducted within a single network to one that needs support from the larger collective.

DAIDS does not have threshold figures in mind. DAIDS is staying with the network approach, but linkages need to occur where necessary. "If we can't assure the second, then the first looks more and more like stovepipes. We need your help to stick with the network approach and make it successful in the different environment that we are working in."

Guiding Principles – Sites

- Domestic networks are likely to resemble current structures, though there is likely to be a reduction in size and a more focused scope
- International sites are likely to be pluripotent and aligned with multiple networks and investigators, depending upon local expertise and capacity

- Core funding for infrastructure and personnel will come from NIAID, internationally funded through a CRO-type contract structure
- The networks will provide supplemental funding to sites to conduct protocol-specific activities

It was asked whether in light of budget constraints the networks were going to be downsized and refocused. It was also noted that there is a need to prioritize the therapeutic agenda and have that drive decision-making rather than have structure and resources determine the research questions.

DAIDS recognizes the importance of domestic funding and that is why it is continuing to make awards to domestic sites through R01s and the networks. A CRO-like mechanism will be the primary vehicle to fund international sites. International investigators may compete for R01 funding but it is expected that most applicants would not receive competitive ratings from study sections at this point in their development. This funding approach is being more flexible and easier for the international sites.

Most international investigators do not want to be the junior partner in a relationship; they prefer to have funds distributed directly to them from the AACTG rather than through a university. Many have had the experience working for pharmaceutical companies and prefer not to duplicate that experience.

DAIDS will not be taking over direct management of international trial activity. The networks excel at deciding research questions and peer-to-peer education; but international sites require sustained long-term capacity building and that can best be channeled through this initiative.

In discussion, it was stated that it is "supremely paternalistic" to suggest that all international investigators would not be competitive in peer review competition for R01s.

The CRO-like pipeline would fund core activities and the international sites would be encouraged to participate in network protocols to the extent they wish. They also may apply for R01 and other funding sources. DAIDS noted that feedback from international investigators has been encouraging.

It was suggested that this has "come full circle" from the approach a decade ago with HIVNET, and noted that the PACTG and AACTG essentially do this through their funding of core activities such as operations and data centers. However, it was commented that domestic institutions have a huge grants administration support structure and this approach may simplify the application and administrative burden for international investigators.

DAIDS staff reiterated that they are trying to simplify the process of providing core funding while "trying to stay out of the business of deciding science."

The concept of two streams of funding had some support. The importance in maintaining one-on-one peer contact and in guaranteeing autonomy for sites was recognized. However, there was a suggestion to possibly broaden the definition of a site so that it might include a single investigator.

One investigator noted that this initiative would push international sites toward pluripotent research at each site, something that is not done with domestic sites. The capacity of most of those sites to take on such a load was questioned.

It was noted that sites have greater or lesser capacity to do so, but that they should be offered that choice, and respond to local conditions and pressures to take on what they wish and can negotiate with partners. Domestic sites will not be funded through a CRO-like mechanism.

A process will have to be established to select sites that will receive this support. It likely will involve consultations with the networks to define selection criteria, make allocation decisions, and conduct performance reviews. It is likely that existing network sites will be grandfathered into the new program, though the levels of support likely will differ from site to site.

Concern was raised that a lot of linkage with investigators will be lost through the CRO-like mechanism of core funding, and that the protocols will not be sufficient to provide and strengthen those links.

In addition, it was noted that many sites currently are affiliated with only one network. The process would have to articulate the process by which affiliations can expand. Funding cannot be based simply upon patient caseload but must also take into account what the site brings to the table, including leadership.

There was discussion on the strengths and weaknesses of contracts as a funding mechanism. Some felt that contracts have been more difficult to administer, in part because of the difficulty of getting a sign-off by NIAID. DAIDS said that in general modifications and supplemental funding are easier to implement through a contract than a grant.

DAIDS wants to give local investigators the ability to pursue the research that their local public health crisis requires. “We want to make them free agents” in the research agenda. It wouldn’t necessarily be bad to have a little competition between networks for the allegiance of a site. DAIDS prefers to develop core capacity that can be used across functional areas of research without having those tied to the “stovepipes” of specific trial activities. The CRO-like entity would not have its own autonomous agenda aside from helping local investigators build and sustain research capacity.

It was noted that the operations center did not serve the AACTG well when it was under a contract from DAIDS and was not directly responsible to the network.

A DAIDS vision of the CRO-like entity is like a bank where each of the networks has an account they can draw from. The difference is making sure that DAIDS has the same flexibility and the same accountability without having to get deluged by the number of pass-through indirect costs.

It was thought that all parties were trying to achieve the same goals. The questions were how to control the new entity with sufficient input from the networks so that when they are held accountable “we have someone who is accountable to us to make sure that something happens.”

DAIDS affirmed, “The management of the CRO has to be a joint process between the sites and the networks that are being served by the CRO, and DAIDS.” There has to be a unified approach to management. DAIDS pledged to work with the networks to develop an effective management structure, and called it “a huge piece that has to tie into the whole system.” DAIDS has no desire to micromanage.

One investigator was wary, noting that having separate operations and data management centers has been important to the pediatrics research agenda not being ignored within a broader agenda.

There must be clear guidelines that the CRO is responsible not just to DIADS but also to the networks.

DAIDS reiterated that systems have to be integrated with common standards and administrative mechanisms so as not to overwhelm the international sites.

Another investigator made the case for flexibility to integrate activities when the needs and opportunities arise. The CRO needs "a strong board of directors," including representatives from the networks, in order to accomplish this, set priorities, and not work at cross-purposes to the networks.

DAIDS recognized that there is a tension between the needs of the networks and the investigators.

It was noted that the level of core funding at individual sites might depend upon the networks – some networks may need or choose to associate with researchers that require significantly more core funding for the institution. The networks should be deciding that level of core funding.

Core funding was seen as helping certain sites and networks "stay alive" as they wait for a product such as a vaccine to become available for a phase III trial. It also allows for flexible use of those core resources when there are delays with one trial.

The CRO approach was considered "terrific" by one investigator because it gives flexibility to the investigator on the ground to do the work that local conditions demand but that a network trial may not see as part of their mission to fund. One reason why she is excited with the recent ties to NIAID is that they allow the military research program to move away from just vaccines and also embrace therapeutics. Without this expanded capacity, they likely would have difficulty recruiting sites and participants to vaccine trials. When delays occur, the sites have the capacity to do other things and not simply sit on their hands waiting.

One investigator noted that there was a need for an algorithm by which funding decisions will be made, and anticipated that it might grow out of the report from this network leadership meeting. DAIDS assured the group that the CRO entity would not be autonomous; there will be an interface with the networks.

The network leadership reiterated that the networks have not always been happy with the performance of some of the DAIDS-controlled contractors; "We would like not to repeat that." The management structure must take those concerns into account. It was further mentioned that the real challenge will be for the network leaders to leave their agendas at the door when they meet to make the board of directors type decisions on funding priority for the CRO.

Nonetheless, each function of the CRO, such as banking and operations, would have to be managed differently. The monitoring operations have to be autonomous, but not completely so as they should take guidance from the networks on what the monitoring priorities should be.

Guiding Principles – Laboratories

- Integration of laboratory activities for efficient management and utilization of resources:
    - International: longer term goal to establish regional laboratories supporting multiple networks

    - Locations, infrastructure needs, data management, QA/QC, training/support activities
    - Virology, immunology, pharmacology, diagnostic microbiology/OIs, safety/monitoring
- Core laboratory activities accountable to networks
- Specialized, focused laboratory activities the responsibility of and supported by the networks

It was noted that regional laboratories capable of supporting multiple networks must have broad capacities. Monitoring endpoints of therapeutic clinical trials requires the capacity to perform measures of HIV RNA, CD4 count, viral clades, drug resistance, and immunologic response to therapy. Measurement of immunologic responses and core virology will be important to vaccine trials.

Safety monitoring requires additional capacity to measure chemistry panels and toxicity. A central local or regional lab will be required "so that the sties themselves are not held responsible for QA/QC for this clinical care function."

It was recognized that currently only three sites in South Africa have the expertise to serve as regional immunologic and virologic laboratories for multiple networks, while one in Uganda may be capable of being upgraded relatively quickly. In addition, the military program is building a regional lab in Nairobi, in large measure because of air transit connections, and probably a second site in west central Africa.

Furthermore, the Kampala site is doing a good job with little physical infrastructure, but they are going to be moving to a new facility, which should strengthen their capacity.

Given the planned scope of activity, it was felt that a regional lab in east Africa would be required.

DAIDS asked the group to imagine what labs would need to be in place to conduct: safety monitoring for all; endpoints measurement; and assay development and implementation. It was suggested that perhaps DAIDS should contract for this capacity for all of the networks. Thought should be given to what DAIDS should supply and what the networks should do for themselves.

One investigator felt "Safety should be a centralized function that is made available to the networks in a uniform way." It was also noted that some safety measures may have to be on site for prompt availability of results. Others disagreed that the facility had to be literally on site, but agreed that the response had to be available relatively quickly.

DAIDS said that at a minimum the networks need to develop uniform program safety standards, then the CRO can provide that capacity, and the networks can plug into that service.

Endpoint monitoring likely will differ between the networks, but common regional capacity and standards may be developed. Perhaps therapeutics might focus on virology and vaccines on immunology; perhaps basic assays such as viral load and CD4 count could be contracted out to commercial labs. She noted that researchers initially performed these measures themselves and began to farm them out as commercial facilities demonstrated their capacity to do the work, often more uniformly and for less money.

The group felt strongly that diagnostic microbiology capacity, to screen for and identify coinfections associated with HIV transmission and disease progression, is a necessary component of laboratory capacity.

The fact was raised that host partners often see laboratory capacity as a source of pride; one that allows them to do other things. The allotment of capacity and siting of regional laboratories is a matter that will have to be addressed with some "political" sensitivity.

Laboratory capacity is being built into regional hospitals at DOD trial sites using central laboratories for QA/QC.

Building laboratory capacity "to leave behind" in these regions is an important part of the program. However, DAIDS and the groups warned "a welfare system for virologists" by creating such facilities when the private sector might do an equal or better job for less money, and create greater infrastructure for the actual delivery of care. Others felt that networks should not be building buildings and purchasing machines.

DAIDS urged the networks to work with industry where possible noting that assays must be standardized across networks, in part to minimize the chance of error at labs. Network databases need to be reliable and amenable to cross-protocol examination.

Guiding Principles – Data Management / Operations Centers

- Proposed Goals:
    - Databases and formats that facilitate data sharing for cross-protocol and cross-network analysis
    - Databases and data collection systems that do not pose obstacles to effective use by sites working with more than one network
    - Standardization of common data elements, endpoint definitions, formats for data collection where feasible
    - Data sharing with DAIDS Enterprise system.
- Integration, standardization, transparency
- Strongly integrated within the networks and accountable to the networks

Opinions have evolved from a belief that there has to be a single system and a single form – because network and trial needs may differ – to a point where they believe that all of the databases must be able to interface and communicate. During discussion it became clear that while the "front end" may look different, the "back end" of the data processing would be integrated. The consensus from the technical people on the data side is that this is all possible.

There was discussion of anecdotes of how standardization of recording data is not now the norm among the networks.

Other issues were raised of who has access to trial data and when. DAIDS staff said that administrative data is already reported and open. Data from completed trials is available through a central repository. It was also noted that said much of that data has been transferred to the National Technical Information Service (NTIS). DAIDS is not asking for data from ongoing trials.

Concern was expressed that having a CRO manage this function might interfere network-investigator relationships. DAIDS acknowledged that guidance would have to be created for the CRO coordinator as to priorities and timelines so that the coordinator and networks work in consort and not at cross-purposes. That guidance should be created by the networks.

One investigator believed that there had been sufficient discussion for a working group to create a list of short and long-term issues and goals in this are. The draft will be circulated to the full network leadership in time for presentation to the ARAC. The list would then be "fleshed out" in time for the May ARAC meeting.

It was understood by DAIDS that some of the issues of standardization would be easy to resolve while others might require some compromise and perhaps a period of transition. A timeline for awarding the CRO contract could not be shared at this time but the intent is to make the award during the fiscal year 2004.

Concern was express that the plan does not address the "crying need" to develop data management infrastructure in terms of physical and professional capacity at the sites in developing countries.

Specimen Management

The issue was raised that shipping specimens has the to potential "to empty the coffers" very quickly. DOD pays a fee to the embassy and part of that covers use of embassy couriers. However, during discussion the consensus emerged that such an option probably would not be possible with operations involving host country partners.

It was suggested that the networks look at the bar code system for samples that DOD's group has developed.

The storage of samples is a major issue for all of the networks. The AACTG is spending between and half and a million dollars a year for storage/repository facilities. DAIDS said that the NIAID repository contract is coming up for review in FY '06 and the Division is open to discussion on broader use of a central repository.

There was discussion of the variety of anticoagulants used, depending on whether the sample is being saved for virologic or immunologic purposes.

The group was reminded that political considerations and legal restrictions make it difficult and sometimes impossible to ship DNA samples (including PBMCs) across some national borders. That has hampered efforts to create an international library of polymorphisms. This is an issue that the network leadership might address.

There was consensus that training should be standardized for all networks.

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